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EXAMINER	
BALLARD, KIMBERLY	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/724,319	SCHENK, DALE B.	
	Examiner	Art Unit	
	Kimberly Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2008 and 12 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-58,61,63-66,71-79,81,85,86,92-94,97,99,164-191 and 194-217* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-58,61,63-66,71-79,81,85,86,92-94,97,99,164-191 and 194-217* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/24/08; 8/26/08; 8/27/08; 9/25/08; 3/13/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Kimberly Ballard, Art Unit 1649.

Status of Application, Amendments, and/or Claims

2. New claims 210-217 have been added as requested in the amendment filed June 11, 2008. Following the amendment, claims 56-58, 61, 63-66, 71-79, 81, 85, 86, 92-94, 97, 99, 164-191 and 194-217 are pending in the present application.

Claims **56-58, 61, 63-66, 71-79, 81, 85, 86, 92-94, 97, 99, 164-191** and **194-217** are under consideration in the current office action.

Information Disclosure Statement

3. The information disclosure statements (IDS) filed on the following dates have been considered: June 24, 2008; August 26 and 27, 2008 (4 IDS submitted); September 25, 2008 (2 IDS submitted); and March 13, 2009 (4 IDS submitted).

Withdrawn/Moot Claim Rejections

4. The nonstatutory provisional obviousness-type double patenting rejection of claims 97 and 164-182 over claims 164, 168, 173, 175-197, 201, 208-217, and 220-229

of copending Application No. 10/923,474 is rendered moot in view of the fact that Application No. 10/923,474 was abandoned on February 28, 2008.

5. Applicant's arguments, see pp. 17-18, filed June 11, 2008, with respect to the rejection(s) of claim(s) 85 and 204 under 35 U.S.C. 103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, a new ground(s) of rejection is made as necessitated by amendment for newly added claims 210-217. The new ground of rejection, which includes claims 85 and 204 and was necessitated by Applicant's amendment, is given below.

Maintained Claim Rejections

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. The nonstatutory provisional obviousness-type double patenting rejection of claims 56-58, 61, 63-66, 71-79, 85-86 and 92-94 over claims 164-184, 187-207, 210-217, 220-221, and 223-226 of copending Application No. 10/923,469 is maintained for reasons of record and held in abeyance until all other rejections are resolved.

8. The nonstatutory provisional obviousness-type double patenting rejection of claims 97, 99, and 164-182 over claims 164-166, 168-179, 185, and 187-193 of copending Application No. 10/923,471 is maintained for reasons of record and held in abeyance until all other rejections are resolved.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 56-58, 61, 63-66, 71-79, 81, 86, 92-94, 97, 99, 164-191, 194-203, 205, and 207-209 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,589,154 to Anderson (of record), in view of EP 613007 to Becker (of record) and U.S. Patent 5,593,846 to Schenk (of record). The rejection is maintained for reasons of record and for reasons set forth below.

In the response filed June 11, 2008, Applicant argues that the claimed invention would not have been obvious to one of ordinary skill in the art at the time the invention was made. Applicant makes the following points pertaining to the above rejected claims, each of which will be addressed in turn:

1) The Schenk patent ('846 patent) allegedly does not disclose administration of the 266 antibody to a patient for purposes of a diagnosis or otherwise, nor does the patent allegedly propose administering an antibody to a patient or discuss any means of detecting an antibody after administration to a patient (e.g., imaging). Applicant argues that the '846 patent is only directed to *in vitro* used of the 266 antibody, and that an artisan reading the '846 patent at the relevant time would not have viewed it as proposing using the 266 antibody for administration to a patient, nor found rationale to encourage such use.

2) The post-filing art allegedly indicates that the 266 antibody has little propensity to bind plaques compared with its ability to bind soluble Aβ, and that such characteristic allegedly would be undesirable for an antibody being used for diagnosis in a patient –

that is, the 266 antibody allegedly would not have been an antibody of choice for imaging plaques. And even though the Examiner may be correct that such information was not known at the relevant priority date, allegedly it was nevertheless an inherent property of the antibody. The characteristic pathology of Alzheimer's disease is insoluble Aβ in the form of plaques. Therefore, although the ability of the 266 antibody to bind soluble Aβ would have been useful for the types of assays described in the '846 patent, it allegedly would not have been seen as useful for binding characteristic AD pathology.

3) The purported combination of references in which a discussion of detecting soluble Aβ in bodily fluids removed from a patient is redeployed to render obvious a method of treating Alzheimer's disease also allegedly fails to take into account the lack of reasonable expectation of success in providing a treatment to a hitherto untreatable disease. Neither of the primary references allegedly provides any data to show that Alzheimer's disease can be treated or diagnosed by *in vivo* imaging. And Becker is allegedly an entirely prophetic application that has since been abandoned in all jurisdictions, allegedly suggesting that event the owners of the Becker application were not feeling optimistic.

4) Numerous disinterested parties allegedly were not convinced of immunotherapy as a viable treatment of Alzheimer's disease until publication of the first results showing disease modification in an animal model in the present inventor's work in mid-1999. The observers characterized the findings as "surprising", "amazing", or "revolutionary", and such comments are indicative of non-obviousness of the claimed

invention. The evidence is allegedly of value because it includes the unbiased opinions of experts working in the field at the relevant time and is free of the distortions of hindsight reasoning.

5) Whether the cited art provided a reasonable expectation of success is allegedly a different issue than whether the cited art references are themselves enabling. A proposed reference can be enabling, but also be unpredictable because of the nature of the subject matter and because no data are provided to show the method works. A reference that is itself unpredictable allegedly does not render future developments in the field any more predictable unless and until the source of the unpredictability is removed. Thus, the relevant inquiry is whether the success would have been predictable to the artisan as of the filing date. Surprise expressed by such artisans after the filing date is asserted to be evidence that success was indeed not predictable as of the filing date.

6) Certain dependent claims directed to humanized or chimeric forms of the 266 antibody are further distinguished in that the cited art allegedly does not reference a hybridoma deposit or provide sequences of the 266 antibody. Without the provision of a deposited hybridoma or amino acid sequences of the variable domains of the 266 antibody, it would not have been a routine matter to produce a humanized or chimeric version thereof.

7) Claims 94, 164 and 209 - reciting a sustained release composition - are argued to be useful for maintaining a therapeutic concentration of antibody for an extended period. By contrast, in imaging methods, the goal is to have antibody present

at a single point in time when an image is taken. Thus, allegedly there would be not purpose in using a sustained release composition for imaging in a patient.

Applicant's arguments have been fully considered but they are not persuasive. With respect to 1) above, the '846 patent by Schenk needs to be viewed in the context of the combined teachings of all the prior art references. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the context of the other reference teachings, the Schenk patent's disclosure that antibodies specific for the junction region consisting of residues 13-28 of Aβ are useful for the detection of Aβ because they are not cross-reactive with the large amyloid precursor protein (APP) from which Aβ is derived would therefore seem relevant to the skilled artisan. Schenk also describes this region as being important because it contains the site between amino acid residues 16 and 17, which is a target for normal proteolytic processing of APP. The skilled artisan would thus be motivated to use an antibody that binds to residues 13-28 of Aβ, such as the 266 antibody disclosed in this patent, because of the ability of the antibodies to differentiate between Aβ and APP, which would be very useful in the detection of Aβ species for diagnosis or for targeting Aβ versus APP in therapeutic applications.

With respect to 2), it is reiterated that since the evidence presented regarding the preference of the 266 antibody to bind soluble Aβ is post-filing, it would not have been available to the artisan of ordinary skill at the time the invention was made. Regardless

of whether or not such a property is inherent to the antibody, the skilled artisan at the time of filing would have been unaware of such information and to imply that this as-yet unknown property of the 266 antibody would somehow have affected the artisan's choice would indicate improper hindsight reasoning on the part of the Applicant. Irrespective of this argument, relevant art from the time of filing teaches that antibodies which bind to non-aggregated Aβ are also therapeutically beneficial. As set forth in previous actions, Becker et al. teach "conformationally-specific antibodies and antibody fragments which bind to β-amyloid (Aβ) peptides in a secondary structure-specific manner and the use of these antibodies for the treatment of amyloid diseases, such as Alzheimer's disease. Some of these antibodies bind only those β-amyloid peptides which are predominantly in a β-sheet conformation. A second set of these antibodies bind only those β-amyloid peptides which have adopted a random coil or α-helix conformation" (column 5, lines 42-50; column 7, lines 49-52). Becker et al. teach that the antibodies can be humanized or made chimeric (column 5, lines 50-58). Although Becker et al. may not explicitly state that the β-sheet conformation of Aβ is the predominant aggregated form of Aβ and the α-helix conformation is predominantly found as the soluble or dissociated form of Aβ, the reference inherently teaches so and would have been evident to one of skill in the art. Such knowledge was known in the art at the time of filing, which is evident in the art of record such as in Solomon et al. (*Proc Natl Acad Sci, USA*, Jan 1996; 93:452-455; listed on IDS filed 08/20/2001), which will be discussed in greater detail below. Thus, Applicant's assertion of lack of therapeutic use for an antibody that preferentially binds the soluble form of Aβ is not persuasive

because the artisan would still recognize that antibodies capable of binding to the α-helix conformation of Aβ (i.e., the soluble form of Aβ), are potentially therapeutically useful.

Points 3) lack of reasonable expectation of success and 4) surprise of unbiased observers to therapeutic efficacy of immunotherapy at the time of filing, will be addressed together. Applicant's arguments on these points have been fully considered but are not found persuasive. The aspect that the unbiased artisans in the field found so surprising and unexpected in the June 1999 paper by Schenk was that immunotherapy was effective in an animal model of Alzheimer's disease (AD). While the specific experiment reported by Dr. Schenk's research group in 1999 was directed to administration of Aβ peptides rather than antibodies, the general hypothesized therapeutic mechanism is the same in either case: that antibodies, either made by the host through active immunotherapy or administered exogenously through passive immunotherapy, will have a therapeutic effect. However, this same allegedly "surprising" approach is exactly what Becker teaches. At column 7, lines 39-52, Becker specifically teaches that Alzheimer's disease is to be treated by administering antibodies that bind to Aβ. And Becker et al. are not alone in their view, as other unrelated researchers in the art at the time of filing similarly proposed the use of immunotherapy for the treatment of AD. For example, US Patent No. 5,688,651 to Solomon (issued November 18, 1997; of record) is directed to the inhibition of β-amyloid aggregation using anti-aggregating molecules, such as monoclonal or single-chain antibodies, for the treatment of Alzheimer's disease (column 16, lines 15-33). This view is reiterated in Solomon's

later work (1996 *PNAS* paper, as above), which explicitly proposes the use of monoclonal antibodies and genetically engineered fragments thereof for the treatment of AD (see abstract and p. 454). Immunotherapeutic approaches for the treatment AD at the time of filing for the instant application can also be found in the teachings of U.S. Patents 5,986,054 to St. George-Hyslop et al. (issued November 16, 1999; of record; see column 5, lines 1-5), U.S. Patent 5,753,624 to McMichael et al. (issued May 19, 1998; of record; see column 6, lines 18-24), and Bickel et al. (*Bioconjugate Chem.* 1994; 5:119-125; of record) who note that humanization of monoclonal antibodies targeted against Aβ may facilitate their use as neurodiagnostic or therapeutic agents for Alzheimer's disease (see Abstract and p. 124, 2nd column). Thus, the concept of immunotherapy for the treatment of AD was hardly a surprising therapeutic approach, and would have been known to one of skill in the art at the time of filing.

Thus, contrary to Applicant's assertions that there would be no reasonable expectation of success, the above prior art references illustrate that the field was replete with examples directed to an immunotherapeutic approach to the treatment of Alzheimer's, and therefore the Becker reference would have been expected to achieve successful results if followed accordingly. It is noted that the claimed invention differs from the Becker reference only by specifying the specific binding epitope for the anti-Aβ antibody. For the reasons set forth above and previously, use of an antibody which specifically binds to an epitope within Aβ13-28, such as mAb 266, would have therefore been obvious for diagnostic or therapeutic use.

With respect to 5) above, Applicant argues that since the technology of treating Alzheimer's disease was unpredictable at the time the invention was made, the predictive value of either the Anderson or Becker references would have been low because neither provide supporting evidence of *in vitro* or *in vivo* efficacy. However, Applicant has provided no evidence that the prior art references in question (particularly Becker) are inoperable. Absent such evidence, the references are presumed operable. And although Applicant alleges that a prophetic reference can be enabled but not predictable due to the nature of the art, predictability in the art is a fundamental principle of determining enablement – the two concepts are inexorably linked. Therefore, if a reference teaching is presumably enabled, the results of using such specific teachings would also presumably be predictable. Moreover, the prior art reference need not disclose actual success in terms of clinical trials in order to be enabling, or in this case, predictive. See MPEP § 2121(III) which states that

> A prior art reference provides an enabling disclosure and thus anticipates a claimed invention if the reference describes the claimed invention in sufficient detail to enable a person of ordinary skill in the art to carry out the claimed invention; "proof of efficacy is not required for a prior art reference to be enabling for purposes of anticipation." *Impax Labs. Inc. v. Aventis Pharm.Inc.*, 468 F.3d 1366, 1383, 81 USPQ2d 1001, 1013 (Fed. Cir. 2006).

While that discussion is on point to anticipation, the same logic applies to determinations of a prior art reference under an obviousness rejection. With the exception of the specific binding epitope of the antibody, Becker teaches every element of the claimed invention of independent claims 56, 97 and 183. Becker teaches the artisan of ordinary skill that Alzheimer's can be treated by administering antibodies against Aβ, including chimeric, humanized, and human antibodies. While the field of

Alzheimer's disease treatment was certainly difficult in the 1990s, and in fact remains difficult today, the lack of explicit data supporting the teachings of Becker does not mean that the reference is not enabling or otherwise predictive, particularly when viewed in the context of the other noted prior art references which all indicated that immunotherapy for the treatment of AD was a valid therapeutic approach.

With respect to 6) above, Applicant argues that humanized or chimeric antibodies require the cDNA encoding the antibody, which are obtained from a hybridoma producing the antibody. However, this argument is not persuasive because using only a sample of the monoclonal antibody it is possible to determine the cDNA sequence of the variable regions, which comprises antigen-binding sites of the mouse monoclonal that are grafted into a human antibody framework. Techniques for determining the antigen-binding region of an antibody were well-known at the time of filing. For example, the technique of Edman degradation (as noted in Becker reference at column 3, lines 52-57) can be used to determine the amino acid sequence of a peptide, such as a peptide fragment comprising the antigen-binding region of an antibody (such as an Fv fragment). Accordingly, the artisan could then decipher the DNA encoding the antigen-binding region, position the encoding DNA into a human acceptor antibody framework, and produce a humanized or chimeric 266 antibody. Such knowledge on the production of humanized and chimeric antibodies was also well-known in the art at filing (see, for example, U.S. Patent 5,530,101 to Queen et al. and EP 626390 A1 to Adair et al., both of record).

Finally, with respect to 7) above, Applicant argues that limitations directed to a sustained release composition would not be desirable for *in vivo* imaging diagnostics, and therefore would not be obvious. However, as the disclosure by Becker is not limited to diagnosis of Alzheimer's disease, but also teaches treatment of AD comprising administration of humanized, chimeric or human anti-Aβ antibodies, it would have been obvious to use a sustained release composition. The skilled artisan would know that Alzheimer's disease is a chronic condition and would therefore require prolonged therapy over a period of weeks, months, or even years. As such, a sustained release composition would be highly desired to maintain a therapeutically effective level of antibody in the body.

Accordingly, the rejection of claims 56-58, 61, 63-66, 71-79, 81, 86, 92-94, 97, 99, 164-191, 194-203, 205, and 207-209 under 35 U.S.C. 103(a) is maintained.

New Claim Rejections, Necessitated by Amendment

Claim Rejections - 35 USC § 112, second paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 214 and 215 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "two weekly" in line 2 of each of the claims renders the claims indefinite because it is unclear whether the interval is meant to be once every two weeks or twice per week. The metes and bounds of the claim thus cannot be determined.

Claim Rejections - 35 USC § 103

13. Claims 56, 58, 61, 63-66, 71-76, 81, 86, 92-94, 97, 164-183, 185-191, 194-199, 203, 205, 207-209 and 212-215 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,303,567 B1 to Findeis et al. (issued October 16, 2001, filed August 27, 1996; listed on IDS filed 04/27/2004) in view of Solomon et al. (*Proc Natl Acad Sci, USA*, Jan 1996; 93:452-455; listed on IDS filed 08/20/2001) and EP 613007 by Becker (published August 31, 1994; of record).

Claim 56 and dependent claims thereof are drawn to a method of treating a patient having Alzheimer's disease, comprising administering to the patient an effective dosage of a pharmaceutical composition comprising a human, chimeric or humanized antibody that specifically binds to an epitope within residues 13-28 of Aβ and a pharmaceutical carrier, and thereby treat the disease in the patient. Claim 97 and dependent claims thereof are drawn to a pharmaceutical composition comprising a human or humanized antibody which specifically binds to an epitope within residues 13-28 of Aβ and a pharmaceutical carrier. Claim 183 and dependent claims thereof are directed to a method of reducing risk or delaying onset of Alzheimer's disease in a patient at risk of the disease, comprising administering to the patient an effective

dosage of said pharmaceutical, thereby reducing the risk or delaying the onset of the disease in the patient.

Findeis et al. teach modulator compounds, and pharmaceutical compositions thereof, that bind to natural β-amyloid peptides (β-APs), modulate the aggregation of natural β-amyloid peptides and/or inhibit the neurotoxicity of β-APs (column 4, lines 26-31). At column 1 Findeis teaches that Alzheimer's disease is characterized pathologically by the presence of distinctive lesions in the victim's brain, wherein the lesions include abnormal intracellular neurofibrillary tangles and extracellular aggregated amyloid deposits called plaques. β-AP deposition, therefore, is suggested to precede and contribute to the destruction of neurons in the AD brain. In further support of direct pathogenic role for β-AP, Findeis notes that β-amyloid has been shown to be toxic to mature neurons, both in culture and *in vivo*. Findeis therefore discloses the selection of modulator compounds for ability to bind β-AP, modulate its aggregation *in vitro* or *in vivo*, and/or inhibit the neurotoxicity of β-AP fibrils (column 4, lines 54-67). Findeis also notes at column 5, lines 23-26 that all compounds having the property of binding to β-amyloid fibrils and/or modulating the aggregation of the fibrils are intended to be encompassed by the invention.

The modulators are preferably designed based upon the amino acid sequence of the "Aβ aggregation core domain" (ACD) of β-amyloid, which is disclosed as a subregion of natural β-AP that is less than 15 amino acids in length and encompasses the core sequence of amino acid residues 17-20 or 17-21 of β-AP ($A\beta_{17-20}$ and $A\beta_{17-21}$, respectively) (column 8, lines 25-57). The amino acid sequence of $A\beta_{17-20}$ and $A\beta_{17-21}$

are LVFF and LVFFA, respectively. It is noted that the instantly claimed epitope of residues 13-28 of Aβ comprises this ACD amino acid sequence.

Findeis teaches pharmaceutical compositions comprising the modulator compound in a therapeutically or prophylactically effective amount sufficient to alter, preferably inhibit, Aβ aggregation and/or neurotoxicity (column 22, lines 1-9). Findeis discloses that a "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result, such as reduction or reversal of Aβ deposition or neurotoxicity (column 22, lines 10-19). With respect to the dosage, it is taught that dosage values may vary with the severity of the condition to be alleviated, and further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering the compositions (column 22, lines 50-56). As such, Findeis teaches that dosage regimens may be adjusted to provide the optimum therapeutic response. For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation (column 22, lines 62-67). Such optimization of dosage regimen is routine in the art. Therefore, absent evidence of unexpected results, limitations in the present claims directed to multiple dosages over a period of at least 6 months (claims 93, 208), intervals between weekly and every six months (claims 212, 213), and intervals of weekly, two weekly, monthly or between three and six months (claims 214, 215) would fall within the routine optimization discussed by Findeis in adjusting for individual need

for achieving an optimum therapeutic result and would therefore be obvious to one of skill in the art.

Further, the pharmaceutically acceptable carrier taught by Findeis includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible (column 23, lines 15-19), thus meeting limitations of instant claims 165 and 179. The carrier can be suitable for intravenous, intraperitoneal, intramuscular or oral administration (column 23, lines 22-25), which addresses claims 92, 171 and 207. Findeis also discloses that sterile therapeutic compositions can be formulated as a solution, microemulsion, lipsome, or other ordered structure suitable to high drug concentration (column 23, lines 36-39), thus addressing claims 180 and 181. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., propylene glycol, polyethylene glycol), and suitable mixtures thereof (column 23, lines 39-43), thus addressing limitations of instant claims 172-175. The composition may also comprise surfactants, sugars, polyalcohols, modulators for time release formulations, and biodegradable, biocompatible polymers such as polyglycolic acid, polylactic acid, and copolymers among others (column 23, lines 43-64), which addresses claims 94, 164, 169, 170, 176-178 and 209. Findeis also teaches that the composition may be freeze-dried to yield a powder suitable for preparation of sterile injectable solutions (column 24, lines 5-10), thus addressing claim 182.

Finally, Findeis discloses a therapeutic method of administering the disclosed modulator compounds to inhibit Aβ aggregation or prevent the formation of neurotoxic

Aβ fibrils in a subject, such as for the treatment of disorders associated with β amyloidosis (e.g., Alzheimer's disease) (column 28, lines 10-36). In a preferred embodiment, the method is used to treat Alzheimer's disease (e.g., sporadic or familial AD, including both individuals exhibiting symptoms of AD and individuals susceptible to familial AD) (column 29, lines 12-15). Such disclosure of patient populations amenable to the therapeutic methods would address recited limitations within claims 56 and 183 (regarding treatment of a patient having Alzheimer's disease or reducing the risk or delaying onset of Alzheimer's disease in a patient at risk of the disease), claims 61 and 186 (a human patient), claims 63, 64, 188, 189 (patient is under 50; patient has inherited risk factors – i.e., both encompassed by treatment of familial AD, which is characterized by early disease development), claims 65 and 190 (patient has no known risk factors for AD – i.e., sporadic AD), and claim 187 (patient is asymptomatic).

In summary, Findeis et al. teach methods and pharmaceutical compositions for the treatment of Alzheimer's disease comprising administering a therapeutically effective amount of a modulator compound that binds to the Aβ aggregation core domain ($A\beta_{17-20}$ or $A\beta_{17-21}$) and inhibits aggregation of Aβ fibrils and/or inhibits neurotoxic fibril formation, as well as suitable methods for determining and selecting for such modulatory agents (see, for example, the Neurotoxicity Assay at columns 43-44). The difference between the disclosure by Findeis et al. and the claimed invention is that the reference does not teach that the modulator compounds are antibodies, such as a human, chimeric or humanized antibody, or specific binding fragments thereof.

Solomon et al. teach the use of monoclonal antibodies directed against β-amyloid as being capable of binding to and inhibiting the aggregation of β-amyloid peptides *in vitro* (see abstract). In line with the teachings of Findeis et al., Solomon notes at page 454, 2nd column, that because β-amyloid peptide (i.e, β-AP or βA4) has been shown to be produced in a soluble form in normal individuals, the aggregation of soluble β-AP into insoluble amyloid fibrils is believed to be a crucial step in the pathogenesis of Alzheimer disease. Therefore, to reduce or eliminate the extent of pathological protein depositions in the brain, Solomon continues, much effort has been focused on developing potent and selective inhibitors of β-amyloid aggregation. Solomon therefore teaches that preparing monoclonal antibodies against "aggregating epitopes," identified as sequences related to the sites where protein aggregation is initiated, may provide a tool for preventing the phenomenon of protein aggregation. Solomon indicates that the β-AP residues His^{13} and His^{14} may be implicated in β-sheet formation of β-AP (which leads to aggregation), and the site defined by residues 12-17 of β-AP may also be involved. Solomon therefore suggests that anti- β-AP monoclonal antibodies may be used *in vivo* to prevent the β-amyloid peptide aggregation that is associated with Alzheimer's disease (see abstract). Further, Solomon teaches that advances in antibody engineering, such as the production of single-chain antibodies linked to specific signal sequences for intracellular targeting, could provide for potential therapeutic approaches targeted at fibrillar β-amyloid accumulation in Alzheimer's disease (final paragraph on page 454). It is noted that the linkage of a targeting

sequence to a single-chain antibody would address the limitation of claims 86 and 205, reciting that a chain of the antibody is fused to a heterologous polypeptide.

In accordance with the teachings of Solomon, Becker et al. disclose that the β-amyloid peptide is involved in the loss of neuronal cells that occurs in Alzheimer's disease, and similarly notes that β-amyloid peptides are neurotoxic both *in vitro* and *in vivo* (column 1, lines 30-36). And similar to the Findeis et al. reference, Becker teaches a series of assays useful in evaluating the efficacy of agents which inhibit the neurotoxic effects of β-amyloid peptide, wherein the β-amyloid peptide is predominantly of the β-sheet conformation (column 1, lines 52-56). Such compounds include conformationally-specific antibodies and antibody fragments which bind to β-amyloid peptides in a secondary structure-specific manner, such as the β-sheet conformation (column 5, lines 34-50). As noted above, it is the β-sheet conformation which causes β-amyloid peptides to form fibrils which then lead to β-amyloid aggregation and plaque deposition in Alzheimer's disease. Becker teaches the use of antibodies specific for β-amyloid peptides which are predominantly β-sheet in conformation in the treatment of Alzheimer's disease in humans (column 7, lines 26-28 and 39-52). Becker discloses that such antibodies include chimeric, humanized, veneered, resurfaced, or CDR-grafted antibodies, fragments of antibodies (such as Fab, Fab', Fab_2', and Fv fragments), single chain polypeptide binding molecules, as well as human monoclonal and polyclonal antibodies (column 5, line 51 – column 6, line 19), thus addressing limitations of claims 66, 71-76, 81, 191, 194-199 and 203. Becker further teaches genetically engineered antibodies, such as humanized and chimeric antibodies, which

retain the epitope specificity of monoclonal antibodies, are known in the art and are advantageous because they are less immunogenic when administered to humans (column 6, lines 31-40). Becker notes that single chain antibody technology involves joining the binding regions of heavy and light chains with a polypeptide sequence, which again meets the limitation of claims 86 and 205. Becker also teaches pharmaceutical compositions comprising the Aβ-specific antibodies and formulated for parenteral administration (column 8, lines 19-22). For intravenous administration, Becker teaches that the antibody is dissolved in physiological saline, Ringer's solution or a 5% dextrose solution, thus addressing limitations of claims 166-168.

As evidenced by the prior art, the skilled artisan would have known that residues 17-21 and also at least residues 13 and 14 of the β-amyloid peptide are implicated in the neuropathology of amyloid fibril formation leading to amyloid plaque deposition, such as in the brains of Alzheimer's disease victims. One of ordinary skill in the art at the time of filing would have also recognized the value of methods of identifying compounds, such as antibodies, which bind these regions of β-amyloid and inhibit its aggregation and/or reduce its neurotoxicity. Genetically engineered antibodies selected for their ability to specifically bind to the aggregating core domain of Aβ, which is taught to encompass at least residues 13, 14 and 17-21 of Aβ (and more specifically residues 17-20 of Aβ), would therefore be expected to specifically bind to an epitope within residues 13-28 of Aβ (such as in claims 56, 97 and 183). Such antibodies would also reasonably be expected to compete with the monoclonal antibody designated 266 for binding to Aβ, wherein the 266 monoclonal antibody's epitope is noted to be $A\beta_{16-23}$ (as

stated in the Seubert Declaration filed 10/16/2007, paragraph 4). Therefore, it would have been obvious to the skilled artisan to select for antibodies that specifically bind to an epitope within residues 13-21 of Aβ and which inhibit Aβ aggregation, engineer them so that they are less immunogenic to humans (such as chimeric, humanized, or human antibodies), formulate them into pharmaceutical compositions, and use the selected, engineered anti-Aβ antibodies in the treatment of subjects having or at risk of having Alzheimer's disease to yield predictable results.

KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). Rather, an additional rationale for the instant finding of obviousness is that the claims would have been obvious because a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. Utilizing a specifically binding monoclonal anti-Aβ antibody (as in Solomon) instead of a binding peptide (as in Findeis), or a humanized, chimeric, or human antibody (as in Becker) instead of a mouse monoclonal antibody, amounts to a simple substitution of one known, equivalent element for another to obtain predictable results. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Further, as Alzheimer's disease is a chronic neurodegenerative disease in which patients may survive for many years beyond initial diagnosis (or decades even in

patients at risk of the disease but not actually having symptoms or diagnosed) it would have been obvious to optimize their treatment regimen over the course of weeks, months, or years. The various dosage intervals are clearly parameters that a person of ordinary skill in the art would routinely optimize (see MPEP 2144.05). In fact, the disclosure of Findeis et al. explicitly states that such dosage regimens would necessarily need to be adjusted for each individual to provide the optimum therapeutic effect. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal dosage regimen. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of dosage intervals would have been obvious at the time of Applicants' invention. Accordingly the combined teachings of the above references render obvious the instant invention of claims 56, 58, 61, 63-66, 71-76, 81, 86, 92-94, 97, 164-183, 185-191, 194-199, 203, 205, 207-209 and 212-215.

14. Claims 57, 99 and 184 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,303,567 B1 to Findeis et al. (issued October 16, 2001, filed August 27, 1996; listed on IDS filed 04/27/2004) in view of Solomon et al. (*Proc Natl Acad Sci, USA*, Jan 1996; 93:452-455; listed on IDS filed 08/20/2001) and EP 613007 by Becker (published August 31, 1994; of record) as applied to claims 56, 58, 61, 63-66, 71-76, 81, 86, 92-94, 97, 164-183, 185-191, 194-199, 203, 205, 207-209 and

212-215 above, and further in view of US 5,593,846 to Schenk et al. (issued January 14, 1997, of record).

The combined teachings of Findeis, Solomon and Becker are discussed above. The difference between the prior art references and the claimed invention is that the references do not teach the monoclonal antibody 266.

Schenk et al. teach that antibodies specific for the junction region consisting of residues 13-28 of Aβ are useful because they do not cross-react with the larger amyloid precursor protein (APP) from which the Aβ peptide is derived. Schenk discloses the monoclonal antibody 266, which was raised against residues 13-28 of Aβ.

It would have been obvious to one of ordinary skill in the art at the time the invention was filed to use a humanized version of the 266 monoclonal antibody taught by Schenk in the treatment of Alzheimer's disease as taught by Findeis, Solomon and Becker. It is noted that the peptide used to make mAb 266, Aβ 13-28, encompasses the core aggregating domain of Aβ peptide (residues 13-21), as is taught by Findeis and Solomon. The claimed antibody, and therapeutic method thereof, would be obvious because the skilled artisan has good reason to pursue the known options within his or her technical grasp to obtain predictable results. Such would amount to substitution of known equivalent elements, i.e. one antibody for another, to yield predictable results.

15. Claims 85 and 204 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,303,567 B1 to Findeis et al. (issued October 16, 2001, filed August 27, 1996; listed on IDS filed 04/27/2004) in view of Solomon et al. (*Proc Natl Acad Sci,*

USA, Jan 1996; 93:452-455; listed on IDS filed 08/20/2001) and EP 613007 by Becker (published August 31, 1994; of record) as applied to claims 56, 58, 61, 63-66, 71-76, 81, 86, 92-94, 97, 164-183, 185-191, 194-199, 203, 205, 207-209 and 212-215 above, and further in view of EP 0620 276 A1 by Adair et al. (published October 19, 1994).

The combined teachings of Findeis, Solomon and Becker are discussed above. The difference between the prior art references and the claimed invention is that the references do not teach that the isotype of the antibody is IgG1.

Adair et al. disclose generic methods of producing humanized monoclonal antibodies from non-human species in order to reduce immunogenicity of the antibodies when they are administered to a human (p. 3, lines 1-10). Adair teaches that the constant domains of the humanized antibodies may be selected with regard to the proposed function of the antibody, such as when particular effector functions may be desired. For example, Adair notes that IgG human constant region domains may be used, especially IgG1 and IgG3 isotypes, when the humanized antibody molecules are intended for therapeutic uses and antibody effector functions are required (p. 6, lines 54-57).

As evidenced by the Findeis, Solomon, and Becker references, the skilled artisan would have known that humanized antibodies to Aβ would be useful for the treatment of amyloid aggregation diseases, such as Alzheimer's disease. As evidenced by the Findeis et al. and Solomon et al. references, the skilled artisan would have known that residues 13-21 of Aβ comprise the aggregating core domain of Aβ, and that compounds (such as monoclonal antibodies) which specifically bind to this region inhibit Aβ

aggregation and reduce neurotoxicity, and are thus useful for the treatment of Alzheimer's disease. As evidenced by the Adair et al. reference, the skilled artisan would have known that IgG1 would be desirable for humanized antibodies designated for treatment. Given the disclosures of these prior art references, it would have been reasonable to predict that a humanized IgG1 antibody, which binds to an epitope within resides 17-21 of Aβ could be successfully generated and which would be useful in the treatment of Alzheimer's disease. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Becker et al.'s therapeutic humanized antibodies to produce a humanized antibody which binds to residues 17-21 of Aβ, as taught by Findeis and Solomon, to yield predictable results. This is because the artisan has good reason to pursue the known options within his or her technical grasp to obtain predictable results. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

16. Claims 77-79 and 200-202 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,303,567 B1 to Findeis et al. (issued October 16, 2001, filed August 27, 1996; listed on IDS filed 04/27/2004) in view of Solomon et al. (*Proc Natl Acad Sci, USA*, Jan 1996; 93:452-455; listed on IDS filed 08/20/2001) and EP 613007 by Becker (published August 31, 1994; of record) as applied to claims 56, 58, 61, 63-66, 71-76, 81, 86, 92-94, 97, 164-183, 185-191, 194-199, 203, 205, 207-209 and

212-215 above, and further in view of Plückthun (*Immunol Rev*. 1992; 130:151-188, of record).

The combined teachings of Findeis, Solomon and Becker are discussed above. The difference between the prior art references and the claimed invention is that the references do not teach a bispecific antibody or antibody fragments thereof.

Plückthun teaches engineered antibodies that include single chain antibodies, antibody fragments including Fv and Fab fragments (pp. 152-158), bispecific antibodies (pp. 172-177), and humanized antibodies (p. 177). Plückthun discloses that the most efficient way to increase the equilibrium constant of an antibody to a surface is to make use of the multivalency effect (p. 172). Plückthun notes that this is a general principle and thus applies independently of the nature of the antigen and of the binding site. Such bivalent (i.e., bispecific) antibodies and antibody fragments thus constitute the most reliable and efficient way to increase effective binding constants to a given surface (p. 172).

As evidenced by the Findeis, Solomon, and Becker references, the skilled artisan would have known that humanized antibodies to Aβ would be useful for the treatment of amyloid aggregation diseases, such as Alzheimer's disease. As evidenced by the Findeis et al. and Solomon et al. references, the skilled artisan would have known that residues 13-21 of Aβ comprise the aggregating core domain of Aβ, and that compounds (such as monoclonal antibodies) which specifically bind to this region inhibit Aβ aggregation and reduce neurotoxicity, and are thus useful for the treatment of Alzheimer's disease. As evidenced by the Becker et al. reference, the skilled artisan

would have known that humanized, chimeric or human antibodies would be desirable as they are less immunogenic, particularly for therapeutic use in humans. And as evidenced by the Plückthun reference, the skilled artisan would have recognized the benefit of using bivalent (i.e., bispecific) antibodies or bivalent antibody fragments so as to increase binding affinity for a given antigen. Given the disclosures of these prior art references, it would have been reasonable to predict that a bispecific humanized, chimeric or human antibody or bispecific fragment thereof which binds to an epitope within resides 17-21 of Aβ could be successfully generated and would be useful in the treatment of Alzheimer's disease. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Becker et al.'s therapeutic humanized, chimeric or human antibodies to produce a bispecfic antibody or fragment thereof which binds to residues 17-21 of Aβ, as taught by Findeis and Solomon, to yield predictable results. This is because the artisan has good reason to pursue the known options within his or her technical grasp to obtain predictable results. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

17. Claims 210, 211, 216 and 217 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,303,567 B1 to Findeis et al. (issued October 16, 2001, filed August 27, 1996; listed on IDS filed 04/27/2004) in view of Solomon et al. (*Proc Natl Acad Sci, USA*, Jan 1996; 93:452-455; listed on IDS filed 08/20/2001) and EP 613007 by Becker (published August 31, 1994; of record) as applied to claims 56, 58,

61, 63-66, 71-76, 81, 86, 92-94, 97, 164-183, 185-191, 194-199, 203, 205, 207-209 and 212-215 above, and further in view of Trang et al. (*Pharm Res*. 1990; 7(6):587-592).

The combined teachings of Findeis, Solomon and Becker are discussed above. The difference between the prior art references and the claimed invention is that the references do not explicitly teach that the antibody is administered on multiple occasions determined by when the level of antibody has declined to a baseline concentration before treatment or a predetermined percentage of a peak concentration less baseline concentration (claims 210-211), or that the antibody is administered on multiple occasions wherein the dose and frequency of administration are determined from the half-life of the antibody.

Trang et al. teach methods of measuring and evaluating the pharmacokinetics of chimeric monoclonal antibodies (mAbs) administered to humans for the purpose of therapy. Although the chimeric mAbs used in this study, a mouse/human chimeric C-17-1A mAb used for metastic adenocarcinoma therapy, is not the same as the instantly claimed antibody, the reference is presented to demonstrate the knowledge in the art with respect to the use of mAbs for immunotherapy in humans. For example, Trang et al. teach measuring serum concentrations of the chimeric mAb prior to (i.e., a baseline concentration), during administration, and for several days following administration. Trang tested both single treatment and multiple treatment paradigms (one every 2 weeks for a total of 3 doses) at different dosages (10 mg or 40 mg per treatment) (see p. 588). Trang also determined the half-life of the administered antibody (see Table I on p. 589) and correlated a relationship between C-17-1A total-body clearance and tumor

size (see Figure 5, p. 591), which could be used to assess therapeutic efficacy. Thus, one of skill in the art would recognize such methods as being useful for determining the serum concentration and biological half-life of administered antibodies, such as for establishing optimally effective dosage regimens.

As mentioned above, the skilled artisan would be aware that Alzheimer's disease is a chronic neurodegenerative disease in which patients may survive for many years beyond initial diagnosis, and therefore AD patients would necessarily require an treatment period extending over weeks, months or years. As evidenced by the Findeis et al. reference, the skilled artisan would have also known that dosage regimens, including dose and frequency of administration, would necessarily need to be adjusted for each individual to provide the optimum therapeutic effect. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was filed to optimize the dosage regimen a humanized, chimeric, or human anti-Aβ antibody that binds to an epitope within residues 13-28 of Aβ, as taught by Findeis, Solomon and Becker, so as to maintain a therapeutically effective level of antibody in the patient. The administered dose and frequency of administration are clearly parameters that a person of ordinary skill in the art would routinely optimize (see MPEP 2144.05). Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. For example, it would have been customary for the skilled artisan to determine the optimal dosage regimen with respect to clinical safety (to minimize potential adverse effects) and therapeutic efficacy. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of dose and/or

frequency of administration would have been obvious at the time of Applicants' invention. Accordingly the combined teachings of the above references render obvious the instant invention of claims 210, 211, 216 and 217.

Conclusion

18. No claims are allowed.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Ballard whose telephone number is 571-272-2150. The examiner can normally be reached on Monday-Friday 9 AM - 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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